

CORRECTED VERSION

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 October 2001 (04.10.2001)

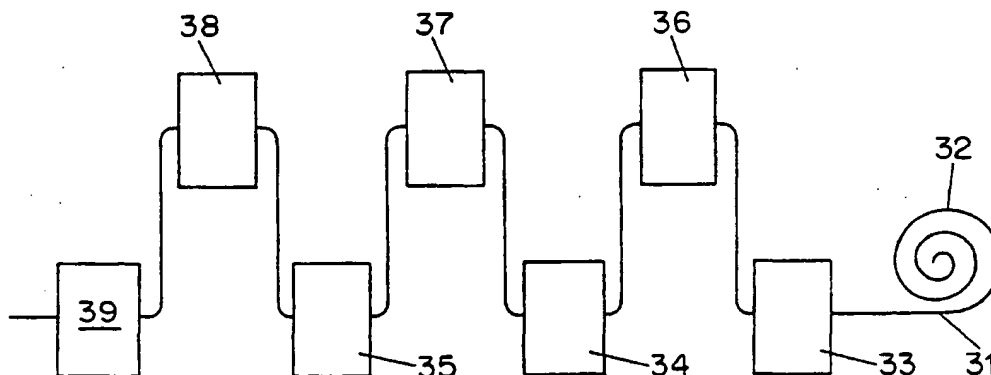
PCT

(10) International Publication Number  
WO 01/73109 A2

- (51) International Patent Classification: C12Q 1/00
- (21) International Application Number: PCT/US01/10097
- (22) International Filing Date: 28 March 2001 (28.03.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
09/537,599 28 March 2000 (28.03.2000) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:  
US 09/537,599 (CON)  
Filed on 28 March 2000 (28.03.2000)
- (71) Applicant (for all designated States except US): INVERNESS MEDICAL TECHNOLOGY, INC. [US/US]; Two University park, 51 Sawyer Road, Suite 200, Waltham, MA 2453-3448 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DAVIES, Oliver, William, Hardwicke [GB/GB]; 15 Drummond Circus, Inverness Circus, Inverness IV2 4QP (GB). MCALEER, Jerome, Francis [GB/GB]; 52 Nobles Close, Grove Wantage OX12 0NR (GB). YEUDALL, Robert, Malcolm [GB/GB]; 5 Stratherrick Gardens, Inverness IV2 4LX (GB).
- (74) Agent: LARSON, Marina, T.; Oppedahl & Larson LLP, P.O. Box 5068, Dillon, CO 80435-5068 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— without international search report and to be republished upon receipt of that report

[Continued on next page]

(54) Title: CONTINUOUS PROCESS FOR MANUFACTURE OF DISPOSABLE ELECTRO-CHEMICAL SENSOR



(57) Abstract: Sensors formed from a substrate, an electrode layer and at least a first reagent layer are manufactured by transporting a continuous web of the substrate past at least two print stations, and printing the electrode layer and the first reagent layer on the substrate. One of the print stations prints the electrode layer on the continuous web of substrate, and the other of the print stations prints the first reagent layer on the continuous web of substrate as it is transported past the print stations. Additional print stations may be included for the printing of insulation layers, glue prints and the like. The order of printing will depend on the structure desired for the sensor, although the electrode layer(s) will frequently be deposited before the reagent layer(s).

WO 01/73109 A2

BEST AVAILABLE COPY



(48) Date of publication of this corrected version:

31 January 2002

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(15) Information about Correction:

see PCT Gazette No. 05/2002 of 31 January 2002, Section

II

- 1 -

## CONTINUOUS PROCESS FOR MANUFACTURE OF DISPOSABLE ELECTRO-CHEMICAL SENSOR

### DESCRIPTION

#### BACKGROUND OF THE INVENTION

This application relates to electrochemical sensors useful for detection and/or quantification of a target analyte in a sample.

Disposable electrochemical sensors for monitoring of target analytes in blood or urine are well known. In particular, electrochemical measurement of the amount of glucose in a small amount of blood using disposable electrochemical sensors and small, portable meters has become a mainstay of many diabetics. These home-use systems permit routine measurements and provide the diabetic with an increased ability to self-manage his or her condition.

The disposable electrochemical sensors used in these devices are generally formed as a series of patterned layers supported on a substrate. Mass production of these devices has been carried out by screen printing and other deposition processes, with the multiple layers making up the device being deposited *seriatim* in a batch process.

Manufacture of disposable electrochemical sensors by these techniques has several drawbacks. First, operation in batch mode is fundamentally inefficient. Multiple steps in the process requires the use of multiple print lines, one for each layer in the device. Not only does this increase the capital expense for the manufacturing equipment it also introduces multiple opportunities for process variation such as variable delays and storage conditions between print steps, as well as variations in the process itself such as registration drift between different process stations. Such process variations can result in poor calibration of some sensor batches resulting in potentially erroneous reading when the electrodes are used.

A potential second drawback arises from a characteristic inherent to screen printing, namely the thickness of the deposited layers. Standard screen printing processes can be used to deposit layers from 1 to 100  $\mu\text{m}$  in thickness. Heat-cured resins can be used to obtain thinner layers of less than 1  $\mu\text{m}$  in thickness. For printing

- 2 -

electrodes, the capability of screen printing to produce layers with these dimensions is beneficial, since the thicker print has greater conductivity. For reagent layers, for example layers of enzymes which are utilized in many disposable electrochemical reactions, however, thick layers are detrimental to the reliable operation of the device. Specifically, because the amount of signal generated by a device of this type depends on the inter-reaction of these reagents and the target analyte within a very narrow region at the electrode surface, the use of reagent layers which extend beyond this region reduces the measured signal by depleting inwardly migrating analyte before it can reach the measurement zone.

In view of these drawbacks, there is a need for a new approach to the manufacture of disposable electrochemical sensors. It is an object of the present invention to meet this need.

It is a further object of this invention to provide a method for manufacturing disposable electrochemical sensors which operates as a continuous process and which provides for deposition of thin reagent layers.

It is a further object of the invention to provide cassettes which incorporate spooled sensors, including spooled sensors manufactured using the method of the invention.

It is a further object of the invention to provide sensors which having an integrated sealing layer which is combination with the substrate produce a sealed sample receiving chamber, thereby protecting the reagents until time of use, which sensors can be made using the method of the invention.

#### SUMMARY OF THE INVENTION

These and other objects of the invention are met by a method in accordance with the invention for manufacturing electrochemical sensors. The sensors comprises a substrate, an electrode layer and at least a first reagent layer. The method comprises the steps of transporting a continuous web of the substrate past at least two print stations, and printing the electrode layer and the first reagent layer on the substrate. One of the print stations prints the electrode layer on the continuous web of substrate, and the other of the print stations prints the first reagent layer on the continuous web

of substrate as it is transported past the print stations. Additional print stations may be included for the printing of insulation layers, glue prints and the like. The order of printing will depend on the structure desired for the sensor, although the electrode layer(s) will frequently be deposited before the reagent layer(s).

5

#### BRIEF DESCRIPTION OF THE FIGURES

Fig. 1A and 1B show two alternative deposition patterns useful in the method of the invention;

10 Figs. 2A and 2B show an exemplary electrochemical sensor which can be manufactured using the method of the invention;

Fig. 3 shows a schematic view of an apparatus for practicing the method of the invention;

15 Fig. 4 shows post-processing of a web printed with sensors to produce sensor spools;

Figs 5A and 5B shows cassettes useful with the sensor spool of Fig. 4, Fig. 5C shows a meter in combination with the cassette of Fig. 5A;

Fig. 6 shows an alternative embodiment of a sensor which can be manufactured using the method of the invention;

20 Figs. 7A and B shows a further alternative embodiment of a sensor which can be manufactured using the method of the invention; and

Figs. 8 A, B and C shows the application of a sealing layer to a ribbon of test strips in accordance with the invention.

#### 25 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for manufacturing electrochemical sensors using a continuous web of substrate transported past a plurality of printing stations for deposition of various layers making up the sensor. The method can be used for making sensors which are directed to any electrochemically-detectable  
30 analyte.

Exemplary analytes of particular commercial significance for which sensors can be made using the method include; glucose, fructosamine, HbA1C, lactate, cholesterol, alcohol and ketones.

5 The specific structure of the electrochemical sensor will depend on the nature of the analyte. In general, however, each device will include an electrode layer and at least one reagent layer deposited on a substrate. As used in the specification and claims hereof, the term "layer" refers to a coating applied to all or part of the surface of the substrate. A layer is considered to be "applied to" or "printed on" the surface of the substrate when it is applied directly to the substrate or the surface of a layer or  
10 layers previously applied to the substrate. Thus, deposition of two layers on the substrate may result in a three layer sandwich (substrate, layer 1, and layer 2) as shown in Fig. 1A or in the deposition of two parallel tracks as shown in Fig. 1B, as well as intermediate configurations with partial overlap.

In the method of the invention, the electrochemical sensors are printed in a  
15 linear array, or as a plurality of parallel linear arrays onto a flexible web substrate. As discussed below, this web may be processed by cutting it into ribbons after the formation. As used in the specification and claims of this application, the term "ribbon" refers to a portion of the printed web which has been formed by cutting the web in either or both of the longitudinal and transverse directions, and which has a  
20 plurality of electrochemical sensors printed thereon.

Figs. 2A and 2B show the structure of an electrochemical sensors for detection of glucose in accordance with in the invention. On the substrate 10 are placed a conductive base layer 16, a working electrode track 15, a reference electrode track 14, and conductive contacts 11, 12, and 13. An insulating mask 18 is then formed,  
25 leaving a portion of the conductive base layer 16, and the contacts 11, 12 and 13 exposed. A reagent layer of a working coating 17, for example a mixture of glucose oxidase and a redox mediator, is then applied over the insulating mask 18 to make contact with conductive base layer 16. Additional reagent layers can be applied over working coating 18 if desired. For example, the enzyme and the redox mediator can  
30 be applied in separate layers.

- 5 -

It will be appreciated that the specific structure shown in Figs. 2A and 2B is merely exemplary and that the method of the invention can be used to manufacture electrochemical sensors for a wide variety of analytes and using a wide variety of electrode/reagent configurations. Exemplary sensors which could be manufactured using the method of the invention include those disclosed in European Patent No. 0 127 958, and US Patents Nos. 5,141,868, 5,286,362, 5,288,636, and 5,437,999, which are incorporated herein by reference.

Fig. 3 shows a schematic view of an apparatus for practicing the invention. A running web of substrate 31 is provided on a feed roll 32 and is transported over a plurality of print stations 33, 34, and 35, each of which prints a different layer onto the substrate. The number of print stations can be any number and will depend on the number of layers required for the particular device being manufactured. Between successive print stations, the web is preferably transported through a dryer 36, 37, and 38 (for example a forced hot air or infra-red dryer), to dry each layer before proceeding to the deposition of the next. After, the final dryer 38, the printed web is collected on a take up roll or introduced directly into a post-processing apparatus 39.

While the most efficient embodiments of the invention will generally use a plurality of print stations as illustrated in Fig. 3 for the printing of different materials, it will be appreciated that many of the advantages of the invention can be achieved with a process in which a single print station is used several times with different print reagents. In particular, benefits of increased throughput and improved print registration are obtained when using the same print station multiple times. Thus, as used in the specification and claims of this application, the phrase "at least two print stations" refers both to embodiments in which two or more distinct print stations are employed and to embodiments in which a common print station is used in several passes to print the required materials onto the substrate.

As noted above, one of the most important parameters to control when printing the various layers of a biosensor is the thickness of the deposited layer, particularly with respect to the reagent layer. The thickness of the printed layer is influenced by various factors, including the angle at which the substrate and the screen are separated. In a conventional card printing process, where the substrate is presented as

- 6 -

individual cards on a flat table, this angle varies as the squeegee moves across the screen, leading to variations in thickness and therefore to variations in the sensor response across the card. To minimize this source of variation, the print stations used in the method of the present invention preferably makes use of cylinder screen printing or rotogravure printing.

In cylinder screen printing, a flexible substrate is presented to the underside of a screen bearing the desired image using a cylindrical roller and moves synchronously with the squeegee. Unlike conventional printing, where the screen moves away from a stationary substrate, in this process the moving substrate is pulled away from the screen. This allows a constant separation angle to be maintained, so that a uniform thickness of deposit is achieved. What is more, the contact angle, and thus the print thickness can be optimized by choosing the appropriate point of contact. By appropriate optimization, the process can be engineered so that the ink is pulled out of the screen and transferred to the substrate much more efficiently. This sharper "peel off" leads to much improved print accuracy, allowing a finer detail print. Therefore smaller electrodes can be printed and smaller overall sensors can be achieved.

The post-processing apparatus 39 may perform any of a variety of treatments, or combinations of treatments on the printed web. For example, the post processing apparatus may apply a cover over the electrochemical devices by laminating a second continuous web to the printed substrate. The post-processing apparatus may also cut the printed web into smaller segments. To produce individual electrochemical devices of the type generally employed in known hand-held glucose meters, this cutting process would generally involve cutting the web in two directions, longitudinally and laterally. The use of continuous web technology offers the opportunity to make electrochemical sensors with different configurations which offer advantages for packaging and use.

As shown in Fig. 4, the printed web can be cut into a plurality of longitudinal ribbons, each one sensor wide. These ribbons can in turn be cut into shorter ribbons of convenient lengths, for example, 10, 25, 50 or even 100 sensors. These ribbons may be rolled into spools and packaged into a cassette which is inserted into a meter









- 10 -

ribbon so that individual test strips are individually sealed and protected from moisture.

5 Figs. 8 A-C relate to ribbons of test strips with a sealing layer. Fig. 8A shows a composite structure comprising a lower layer ribbon of test strips 80 and an upper sealing layer 81. The upper sealing layer 81 is shown partially peeled back to expose the first test element. The upper layer contains apertures 82 through which electrical contact with the underlying test strip can be made. The sealing layer 81 is typically attached to the ribbon 80 using a hot melt or pressure-sensitive adhesive. The meter employed with the sealed test strip ribbon of Fig. 8A would include a mechanism, 10 such as a knife blade, for peeling back the sealing layer 81 to expose the target area of a strip that is about to be used. After use, the used test strip and the peeled back sealing layer may be cut away from the unused portion of the ribbon, for example using a cutter blade integral to the cassette. The used strips and peeled of sealing layer might also be rolled up onto take-up spools within a cassette as shown in Fig. 15 8B, thus avoiding the need for a user to contact used strips directly.

Fig. 8C shows a variation on the structure of Fig. 8C. In this case, the sealant layer serves as one wall of the test strip sample chamber. This geometry has certain advantages, notably that evaporative cooling of the sample (which can lead to erroneously low readings) is reduced. To prepare a test strip on a ribbon of this type 20 for use, a cut is made which opens the end of a chamber formed by the sealing layer 81 and the test strip ribbon 80. In Fig. 8C, separate cut line-types 88 and 89 are shown for separating used devices and for opening a new device, respectively. These cuts can be made at the same type or at different times.

CLAIMS

- 1        1.        A method for manufacturing electrochemical sensors comprising a substrate,  
2        an electrode layer and at least a first reagent layer, said method comprising the steps  
3        of transporting a continuous web of the substrate past at least two print stations and  
4        printing the electrode layer and the first reagent layer on the substrate, one of said  
5        print stations printing the electrode layer on the continuous web of substrate and the  
6        other said print stations printing the first reagent layer on the continuous web of  
7        substrate as it is transported past the print stations.
- 1        2.        The method of claim 1, wherein the print stations are rotogravure print  
2        stations.
- 1        3.        The method of claim 1, wherein the print stations are cylinder screen printing  
2        stations.
- 1        4.        The method of any of claims 1-3, wherein the electrochemical sensors detect  
2        glucose.
- 1        5.        The method of claim 4, wherein the first reagent layer comprises glucose  
2        oxidase.
- 1        6.        The method of any of the preceding claims, wherein the disposable  
2        electrochemical sensors further comprise a second reagent layer which is deposited on  
3        the continuous web substrate by a third print station.
- 1        7.        The method of claim 6, wherein the second reagent layer comprises an  
2        electron transfer mediator.
- 1        8.        The method of claim 7, wherein the electron transfer mediator is ferricyanide.



- 13 -

1 18. The cassette according to claim 17, wherein the electrochemical sensors are  
2 for the detection of glucose.

1 19. The cassette of claim 17, wherein the sensors are manufactured in accordance  
2 with the method of any of claims 1-16.

1 20. An electrochemical sensor for the detection of an analyte such as glucose,  
2 wherein the sensor is printed on a substrate and is covered by a sealing layer, said  
3 substrate and sealing layer cooperating to form a sealed sample-receiving chamber,  
4 and wherein in use the sealed sample-receiving chamber is cut to produce an opening  
5 to the sample-receiving for the introduction of analyte to the sample.





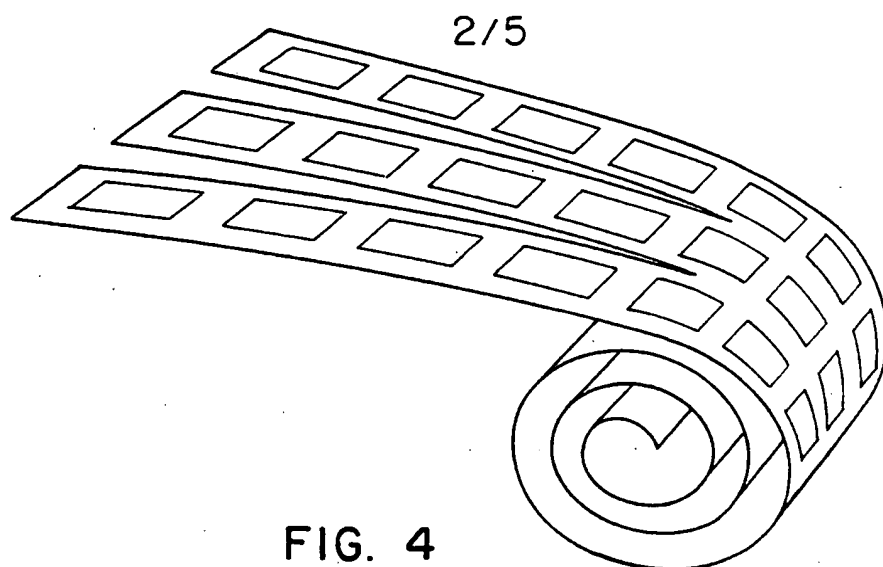


FIG. 4

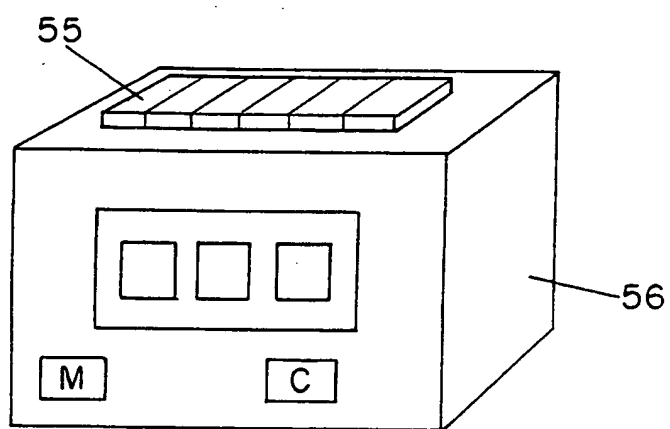


FIG. 5A

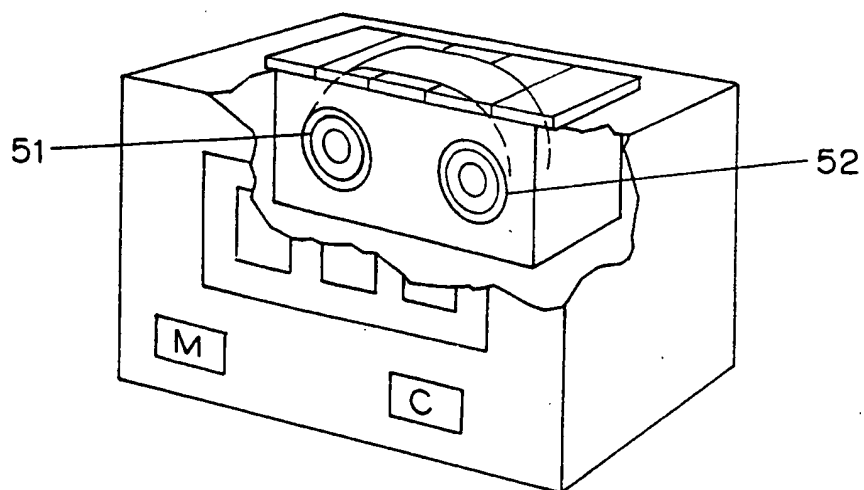


FIG. 5B

3/5

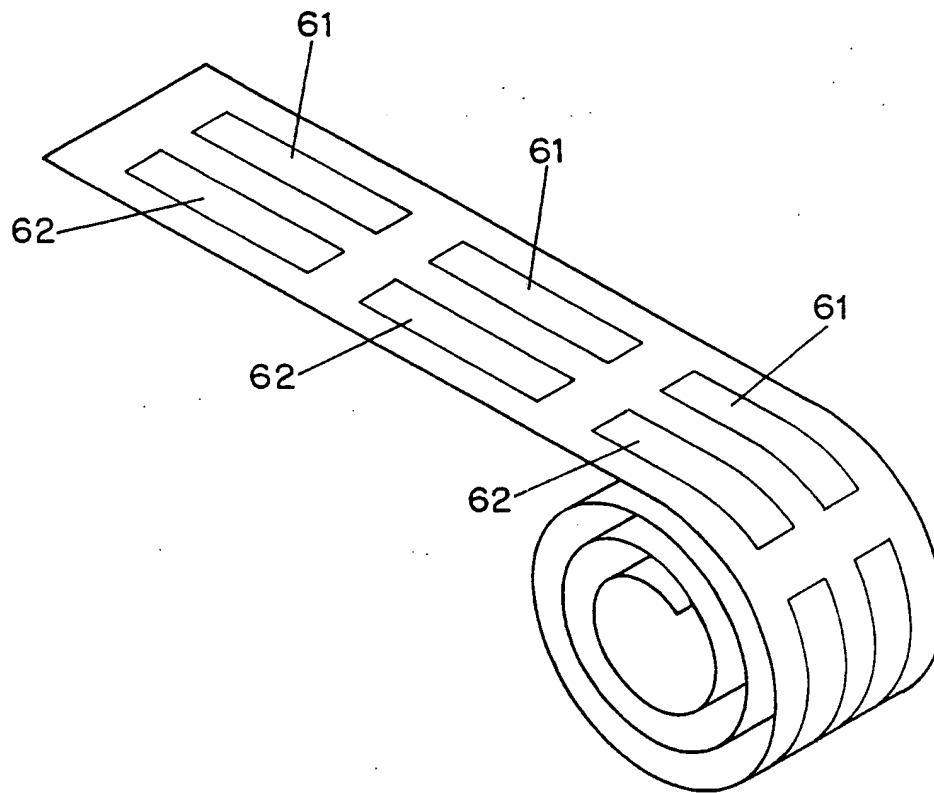


FIG. 6

4/5

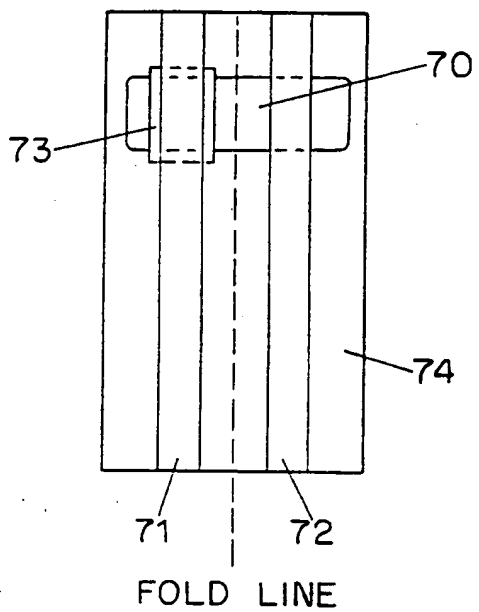


FIG. 7A

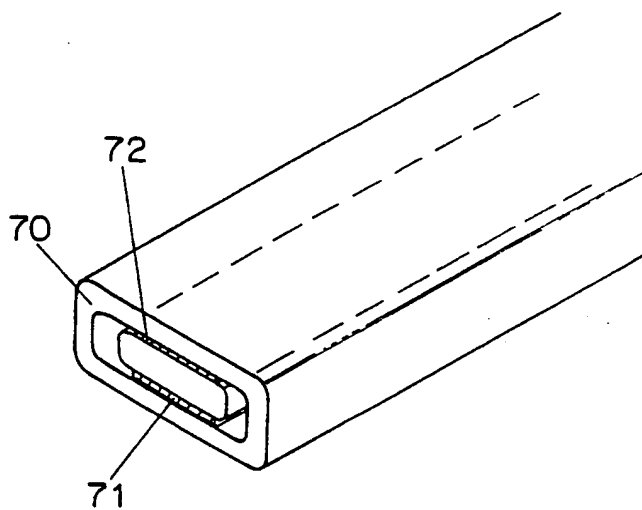


FIG. 7B

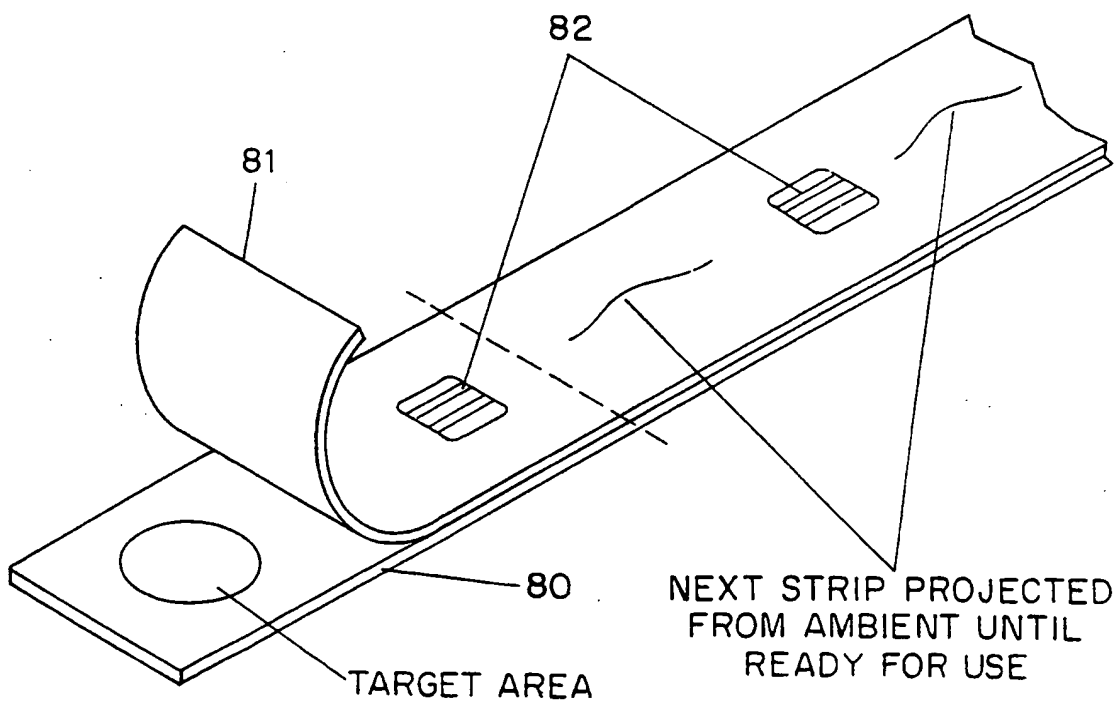


FIG. 8A

5/5

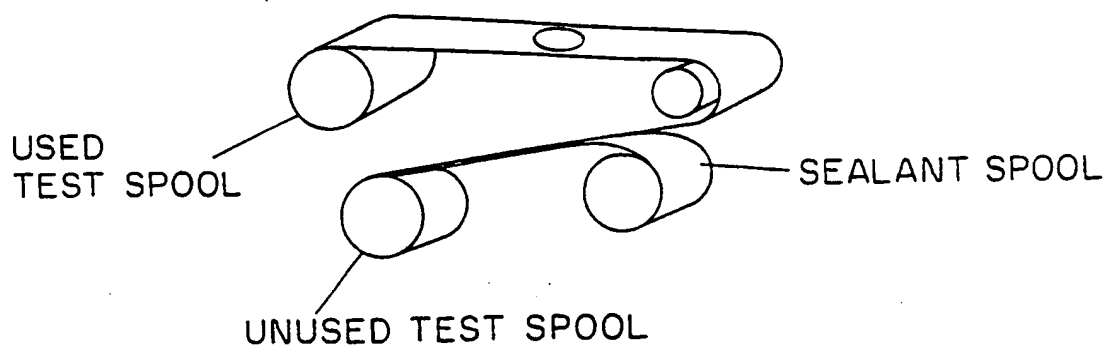


FIG. 8B

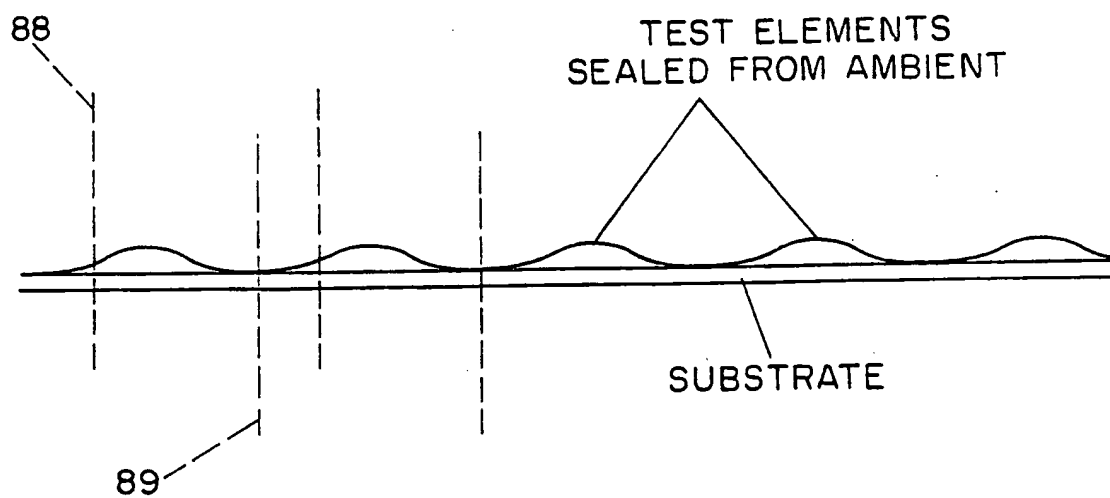


FIG. 8C

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**